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ASSOCIATION OF NEW PERIOPERATIVE BENZODIAZEPINE USE WITH PERSISTENT BENZODIAZEPINE USE

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Abstract

Importance: Increased use of benzodiazepines has resulted in increasing rates of misuse and adverse effects associated with these drugs. Little is known about the initial exposure and source of benzodiazepines among those who use them persistently.

Objective: To examine the frequency of use and persistent use of benzodiazepines among patients undergoing major and minor surgical procedures.

Design, Setting, and Participants: This cohort study included 2 509 599 adult patients who underwent 1 of 11 common surgical procedures from 2009 to 2014 and were recorded in the MarketScan database. The rates of perioperative and persistent benzodiazepine use were examined in benzodiazepine-naive patients.

Results: Among 2 509 599 included patients, the mean (SD) age was 54.4 (15.3) years, and 1 596 137 (63.6%) were women. Perioperative benzodiazepine use was noted in 63 931 patients (2.6%). The median (interquartile range) benzodiazepine supply was 10 (5-23) days. Among benzodiazepine-naive patients prescribed a perioperative benzodiazepine, the rate of persistent benzodiazepine use was 19.5% (95% CI, 19.2%-19.8%). During the 90 to 180–day period after surgery, 7013 of 12 468 patients (56.2%) received 1 prescription for benzodiazepines while 5455 (43.8%) received 2 or more prescriptions. Among patients prescribed a benzodiazepine, persistent use was more common in Medicaid recipients (vs patients with commercial insurance: adjusted rate ratio [aRR], 1.29; 95% CI, 1.03-1.62), patients 70 years or older (vs those aged 40-49 years: aRR, 1.14; 95% CI, 1.05-1.23), in women (vs men: aRR, 1.10; 95% CI, 1.06-1.15), in patients with more medical comorbidities (eg, Elixhauser comorbidity score ≥3 vs 0: aRR, 1.11; 95% CI, 1.04-1.19), and in those with diagnoses of anxiety, depression, insomnia or substance use disorder (eg, with vs without anxiety: aRR, 1.43; 95% CI, 1.37-1.50).

Conclusions and Relevance: In this study, a relatively small percentage of surgical patients were prescribed benzodiazepines in the perioperative period; however, 1 in 5 of these patients went on to persistent benzodiazepine use.

Keywords: benzodiazepine, Frozen elephant trunk, Invaginated intimal mass

Introduction

Benzodiazepines are a class of drugs with sedative, anxiolytic, hypnotic, and anticonvulsant properties. These agents are commonly used for a variety of indications, including anxiety, insomnia, and panic disorders. In the United States, the use of benzodiazepines has increased substantially over the last 2 decades.[1-3] From 1996 to 2013, prescriptions for benzodiazepines increased by 67%, from

8.1 million to 13.5 million prescriptions per year.[1] A cross-sectional survey of adults in 2015 and 2016 reported that 13% of respondents had used benzodiazepines in the prior year.[3]

The increasing rate of benzodiazepine use has been accompanied by a rapid increase in adverse events.[1,4] The rate of overdose deaths from benzodiazepines was 3.07 per 100 000 adults in 2010, a 4-fold increase from 1996.[1] Benzodiazepines are also frequently involved in overdose deaths related to opioids and other synthetic narcotics.[1,5] In addition, benzodiazepines have been implicated in numerous other adverse events, including emergency department visits for accidents, motor vehicle collisions, falls, and fractures.[2,6-8] Benzodiazepines are currently the third most commonly misused illicit substance.[4]

The rise in benzodiazepine prescribing along with drug-related adverse events has led many observers to draw parallels with the opioid crisis.[2] Current estimates suggest that 15% to 20% of benzodiazepines that are prescribed are misused.[3,9] Among individuals misusing benzodiazepine, diversion appears to be common and illicit; synthetic benzodiazepines are becoming more prevalent.[4] However, data on patient acquisition and maintenance of benzodiazepines remain limited. Similarly, how those who use benzodiazepines persistently first acquire these drugs and ultimately go on to prolonged use remains unclear. For opioids, exposure and persistent use of the drugs around the time of surgical procedures are common.[10,11] Theoretically similar patterns may be seen for benzodiazepines, which may be prescribed during the perioperative period for anxiety, insomnia, or nausea. The objective of our study was to determine the prevalence of benzodiazepine prescribing in patients undergoing major and minor surgical procedures. Specifically, we examined the prescription of postoperative benzodiazepines and persistent use of benzodiazepines among those who received prescriptions.

Methods :

Clinical data included age at the time of surgery (ie, <40, 40-49, 50-59, 60-64, 65-69, or ≥70 years), insurance status , self-reported gender (male or female), metropolitan statistical area (MSA; yes, no, or unknown), region , year of the index surgery, and hospital setting (outpatient or inpatient). Preoperative comorbidities were identified by *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes, and comorbidities were estimated using the Elixhauser Index.[18]

We analyzed the occurrence of underlying psychiatric diagnoses including insomnia, anxiety, depression, and substance use disorders (SUDs) during the 12-month period prior to surgery.[10] We identified patients with coding for a diagnosis of cancer from 365 days prior to 180 days after surgery. Adjuvant chemotherapy and radiation after surgery were also captured. We examined opioid use prior to surgery, perioperative opioid use including receipt of a prescription for an opioid during the perioperative period (30 days before to 14 days after), and persistent opioid use, defined as having filled 1 or more opioid prescriptions in the period from 90 to 180 days after surgery in those patients who received a perioperative opioid prescription.[10,17,19,20] We performed sensitivity analyses in which the classification of persistent benzodiazepine use required having filled 2 or more prescriptions in the period 90 to 180 days after surgery or receipt of a 30-day or longer supply of benzodiazepines.

Results:

A total of 2 509 599 patients were identified. The mean (SD) age of the cohort was 54.4 (15.3) years, and 1 596 137 patients (63.6%) were women. Cataract surgery (618 575 [24.6%]) was the most commonly performed procedure, while lobectomy (26 061 [10.4%]) was received by the smallest subgroup of patients. Overall, perioperative benzodiazepine use was noted in 63 931 patients (2.6%; 95% CI, 2.53%-2.57%) . The most commonly used benzodiazepines were diazepam (20 661 [32.3%]) and alprazolam (18 794 [29.4%]). The median (IQR) days' supply of benzodiazepine was 10 (5-23) days, and 35 088 patients (54.9%) filled a benzodiazepine prescription preoperatively . The rate of perioperative benzodiazepine use was 2.5% (95% CI, 2.4%-2.6%) in 2009; it increased in 2010 and 2011 (2011 rate, 2.7%; 95% CI, 2.7%-2.8%) and then declined (2017 rate, 2.6%; 95% CI, 2.4%-2.6%) .

The highest rate of perioperative benzodiazepine use was among patients who underwent lobectomy (1830 of 26 061 [7.0%]) followed by hemorrhoidectomy (5536 of 98 765 [5.6%]), while the lowest rate of use was seen in those who underwent cataract surgery (7230 of 618 575 [1.2%]), appendectomy (1784 of 145 773 [1.2%]), or carpal tunnel surgery (3170 of 182 489 [1.7%]) . Medicaid recipients were 15% more likely to receive a perioperative benzodiazepine prescription than commercially insured patients (5809 of 164 621 [3.5%] vs 58 122 of 2 344 978 [2.5%]; aRR, 1.15; 95% CI, 1.05-1.26). Use of benzodiazepines was lower with older age, among patients who underwent surgery more recently, and among men. Patients with a diagnosis of anxiety, depression, insomnia, SUD, or cancer were more likely to receive a benzodiazepine. Similarly, patients who had used opioids prior to the perioperative period or during the perioperative period were more likely to receive a benzodiazepine prescription.

Among benzodiazepine-naive patients prescribed a perioperative benzodiazepine, the rate of persistent benzodiazepine use was 19.5% (95% CI, 19.2%-19.8%). The rate of persistent benzodiazepine use was 19.9% (95% CI, 19.0%-20.8%) in 2009, increased slightly through 2011 (21.6%; 95% CI, 20.7%-22.5%) and then decreased (2017 rate, 16.0%; 95% CI, 14.7%-17.3%) . During the 90 to 180–day period after surgery, 7013 of 12 648 individuals (56.2%) with persistent benzodiazepine use received 1 prescription for benzodiazepines, while 5455 (43.8%) received 2 or more prescriptions . Alprazolam was the most commonly used benzodiazepine (4619 [37.5%]) during this period, followed by lorazepam (3383 [27.4%]) . The median (IQR) days' supply of benzodiazepine during this period was 30 (15-60) days.

Medicaid recipients were 29% more likely to persistently use benzodiazepines than participants with commercial insurance (1547 of 5809 [26.6%] vs 10 921 of 58 122 [18.8%]; aRR, 1.29; 95% CI, 1.03-1.62) . Persistent use of benzodiazepines was most common after lobectomy (536 of 1830 [29.3%]), colectomy (1086 of 4059 [26.8%]), and cholecystectomy (2195 of 9764 [22.5%]). Persistent benzodiazepine use was more common in women than in men (9143 of 44 240 [20.7%] vs 3325 of 19 691 [16.9%]; aRR, 95% CI, 1.10; 1.06-1.15), among older patients (≥70 years vs 40-49 years: 1147 of 5622 [20.4%] vs 2636 of 13 782 [21.6%]; aRR, 1.14; 95% CI, 1.05-1.23), among residents in the South compared with the Northeast (4683 of 23 224 [20.2%] vs 1650 of 9308 [17.7%]; aRR, 1.16; 95% CI, 1.10-1.23), in patients with more medical comorbidities (eg, with Elixhauser comorbidity score ≥3 vs 0: 1044 of 3840 [27.2%] vs 7229 of 40 433 [17.9%]; aRR, 1.11; 95% CI, 1.04-1.19), and for those who underwent an inpatient procedure compared with outpatient procedure (6015 of 30 115 [20.0%] vs 6453 of 33 816 [19.1%]; aRR, 1.07; 95% CI, 1.01-1.12). Patients with a diagnosis of cancer and those who received chemotherapy or radiation were also more likely to persistently use benzodiazepines. Similarly, diagnoses of anxiety, depression, insomnia, and SUD were all associated with an increased rate of persistent benzodiazepine use (eg, anxiety: 3168 of 11 048 [28.7%] vs 9300 of 52 883 [17.6%]; aRR, 1.43; 95% CI, 1.37-1.50).

Patients who initially received a higher total dose of benzodiazepines (eg, ≥30 mg vs <6 mg: 6651 of 20 132 [33.0%] vs 1230 of 14 539 [8.5%]; aRR, 3.66; 95% CI, 3.44-3.90), a higher daily dose of benzodiazepines (eg, ≥2.0 mg/d vs <1.0 mg/d: 5210 of 23 309 [22.4%] vs 2304 of 14 390 [16.0%]; aRR, 1.35; 95% CI, 1.28-1.41), and a longer duration prescription of benzodiazepines (eg, ≥23 days vs <5 days: 5792 of 16 150 [35.9%] vs 1208 of 14 189 [8.5%]; 3.88; 95% CI, 3.64-4.13) were more likely to persistently use benzodiazepines. Similarly, patients who received a benzodiazepine prescription in the 30-day period prior to surgery and those who received more than 1 benzodiazepine prescription perioperatively more commonly went on to persistent benzodiazepine use. Persistent benzodiazepine use was also more common among patients who used opioids persistently .

Discussion

These data suggest that while a relatively small percentage of surgical patients are prescribed benzodiazepines in the perioperative period, 1 in 5 of these patients will go on to persistent benzodiazepine use. In addition to clinical characteristics, patterns of benzodiazepine prescribing are strongly associated with persistent use and are a potentially modifiable factor to reduce persistent benzodiazepine use.

Population-level data suggest that benzodiazepine misuse is becoming an increasingly important public health challenge.[1-3] From 1996 to 2013, the death rate from overdose involving benzodiazepine increased by more than 400%.[1,4] While the death rate from benzodiazepine overdose plateaued after 2010, perhaps related to efforts focused on opioid safety, death rates have continued to increase for older adults as well as Black and Hispanic populations. Over the same time period, the quantity of benzodiazepines filled per prescription more than doubled.[1] Among patients newly exposed to benzodiazepines at the time of surgery, we noted a substantial risk of continued use after the acute perioperative period. These findings mimic what has been described for opioid use and suggest that surgical procedures may serve as an important exposure for persistent benzodiazepine use.[10,19,21]

Prior studies have shown that the potential for misuse is high among patients exposed to benzodiazepines.[4,22-26] One report suggested that prescription of an anxiety medication was associated with a 60% to 90% increased risk of nonmedical use of these drugs.[23] The high rate of benzodiazepine misuse among those exposed to the drug may reflect ease of access to the medications, a greater abuse potential among those who initially use benzodiazepines, and purposeful seeking of benzodiazepine prescriptions among those who intend to misuse the drugs.[4] History of SUD, younger age at receipt of a benzodiazepine prescription, longer duration of use, and a higher frequency of prescription use have all been associated with benzodiazepine misuse.[4,22-26] In line with the high potential for misuse, we noted that a remarkable 20% of benzodiazepine-naive patients who received a prescription in the perioperative period went on to persistently use the drugs.

While misused benzodiazepines may be obtained from a variety of sources, diversion from family members and friends is the most common origin of the drugs.[4,27-29] One survey found that nearly two-thirds of misused tranquilizers were obtained from either friends or family members and that most of these drugs were originally ascertained from a prescription.[4,27] These findings heighten the concern that perioperative benzodiazepines may be an important source of diverted drugs.

Coingestion of benzodiazepines with other drugs, particularly opioids, is common.[30,31] An ecologic time series study found that nearly 10% of opioid recipients were dispensed a concomitant benzodiazepine in 2014.[30] Nearly half of these patients received the 2 prescriptions from the same health care practitioner on the same day.[30] Coingestion of benzodiazepines and opioids is particularly problematic, as benzodiazepines enhance the effects of opioids and increase the risk of overdose and death.[4,31] The increasing rate of benzodiazepines parallels that of the opioid epidemic in that short-term prescription of these agents for medical indications appears to lead to persistent use of the drugs. Our data suggest that perioperative benzodiazepine use is an important source for prolonged and persistent benzodiazepine use. Initial and persistent opioid use were also significantly associated with persistent benzodiazepine use. Encouragingly, the rate of initial and persistent benzodiazepine use appears to be decreasing.

Conclusions

This study found that although a small percentage of surgical patients receive prescriptions for benzodiazepines, 1 in 5 of them go on to use them persistently. From a policy perspective, these data have important implications. To date, misuse of benzodiazepines has received much less attention than misuse of opioids. Our findings suggest that efforts are needed to encourage the judicious use of these drugs after surgery. Benzodiazepines should only be used in patients with a clear indication, and attempts should be made to limit the quantity and duration of use. Similar efforts have been successfully used to reduce perioperative opioid prescription use. When appropriate, alternative medications with less potential for misuse should be strongly considered. Finally, raising awareness among patients, health care practitioners, and policy makers and implementing pragmatic strategies to limit use may help to curb misuse of benzodiazepine associated with perioperative prescribing.

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